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Adverse events of raltegravir and dolutegravir

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Cohort Study Group

Objective: To compare the frequency and risk factors of toxicity-related treatment discontinuations between raltegravir and dolutegravir.

Design: Prospective cohort study.

Methods: All antiretroviral therapy (ART)-naïve and ART-experienced HIV-infected individuals from the Swiss HIV Cohort Study who initiated raltegravir or dolutegravir between 2006 and 2015 were investigated concerning treatment modification within the first year.

Results: Of 4041 patients initiating ART containing raltegravir ($n=2091$) or dolutegravir ($n=1950$), 568 patients discontinued ART during the first year, corresponding to a rate of 15.5 [95% confidence interval (CI) 14.5–16.9] discontinuations per 100 patient-years. Only 10 patients on raltegravir (0.5%) and two patients on dolutegravir (0.1%) demonstrated virologic failure. The main reason for ART discontinuation was convenience expressed as patient's wish, physician's decision, or treatment simplification ($n=302$). Toxicity occurred in 4.3% of patients treated with raltegravir and 3.6% with dolutegravir, respectively. In multivariable analysis, the only independent risk factor for discontinuing ART because of toxicity was female sex (hazard ratio 1.98, 95% CI 1.45–2.71, $P<0.001$).

Neuropsychiatric complaints were the most commonly reported toxic adverse events and more frequent in the dolutegravir ($n=33$, 1.7%) compared with the raltegravir group ($n=13$, 0.6%). Risk of discontinuation for neurotoxicity was lower for raltegravir than for dolutegravir in multivariable analysis (hazard ratio 0.46, 95% CI 0.22–0.96, $P=0.037$).

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Conclusion: In this, large cohort raltegravir and dolutegravir-containing regimen demonstrated a high virologic efficacy. Drug toxicity was infrequent and discontinuation because of neuropsychiatric events within the first year of treatment was only marginal higher with dolutegravir compared with raltegravir. However, monitoring of neurotoxic side-effects of dolutegravir is important.

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Keywords: dolutegravir, HIV, neuropsychiatric adverse events, raltegravir, toxicity

Introduction

Raltegravir and dolutegravir are currently among the most commonly used integrase strand transfer inhibitors (INSTI), which are part of preferred antiretroviral therapy (ART) regimens according to various guideline boards such as the International AIDS Society and the European AIDS Clinical Society [1,2]. Both agents show a very high antiretroviral potency and, in particular for dolutegravir, a very low risk of virologic failure and development of drug-associated resistance. Further beneficial characteristics of both INSTIs are the excellent tolerability, the low interaction potential as well as the excellent penetration into the central nervous system [3,4,5,6]. No specific organ toxicity associated with raltegravir and dolutegravir was identified in randomized clinical trials. Owing to these favorable characteristics, the once-daily administration, and the low dosage allowing for fixed-dosed combination, the use of dolutegravir in the treatment of HIV-infected patients has rapidly increased since the approval in 2013.

However, recent reports, mainly from retrospective data and smaller cohorts, raised concerns about the safety of dolutegravir in real-life settings with higher than expected discontinuation rates, particularly in respect of neuropsychiatric adverse events [7–9,10].

The aim of our study was to compare the frequency and risk factors of discontinuation between dolutegravir and raltegravir because of any reason and more specifically because of toxicity adverse events in a large cohort of HIV-infected individuals.

Methods

Study setting

We analysed the Swiss HIV Cohort Study (SHCS) database, a large prospective and ongoing cohort study in Switzerland with continuous enrolment of HIV-infected individuals of 16 years or older. In the SHCS, basic sociodemographic characteristics, clinical course, ART, reasons for discontinuation or change of the ART regime,

comedication, immunological, and virological data as well as information on comorbidity and coinfections are collected at registration into the study and every 6 months thereafter on standardized protocols. For the present analysis we used SHCS database update of January 2017.

Study population

All HIV-infected individuals participating in the SHCS starting an antiretroviral regime containing raltegravir or dolutegravir combined with appropriate backbone between 1 April 2006 and 31 December 2015 and who had a follow-up of at least 12 months were eligible for this study.

Definitions

Treatment modification was defined as discontinuation or switch of ART within the first year of treatment. Discontinuation was defined as stopping dolutegravir or raltegravir for at least 4 weeks. A switch to another regimen was defined as changing one or more drugs within 4 weeks after stopping ART. The main reason for treatment modification was classified as treatment failure, intolerance, and/or toxic effects, the patient's choice, the physician's decision, and other reasons. Since 2014 more detailed reasons for drug discontinuation were introduced and prospectively collected in the SHCS database, including treatment simplification, concerns about drug interactions and adherence. Toxicity, predominantly from the nervous system was specifically coded detailed as neuropsychiatric toxicity, headache, or peripheral neuropathy.

Statistical analysis

The primary endpoint was the time to first treatment modification (i.e., switch to another antiretroviral regime or discontinuation) during the first year of treatment. Basic sociodemographic characteristics, CD4⁺ cell counts, HIV RNA, and ART were compared using the χ^2 test for categorical and Mann–Whitney U or Kruskal–Wallis test for continuous variables. We used Kaplan–Meier curves to describe the cumulative incidence of treatment modification according to either raltegravir or dolutegravir-containing ART regimen, and the curves were compared using log-rank tests. Uni and

Table 1. Baseline characteristics of the study population with raltegravir and dolutegravir containing antiretroviral regimen (*n* = 4041) and reasons for treatment modification.

	Raltegravir <i>N</i> = 2091		Dolutegravir <i>N</i> = 1950		<i>P</i> value
	<i>n</i>	%	<i>n</i>	%	
Male	1474	70.5	1455	74.6	0.003
Age, median (IQR)	48	41–54	48	40–54	0.447
White ethnicity	1752	83.8	1566	80.3	0.004
Risk					
MSM	887	42.4	997	51.1	
Heterosexual	723	34.6	679	34.8	<0.001
PWID	245	11.7	107	5.5	
Other	236	11.3	167	8.6	
Prior AIDS-defining condition	623	29.8	381	19.5	<0.001
HCV coinfection	641	30.7	377	19.3	0.001
CD4 ⁺ cells per µl					
<350	713	34.1	341	17.5	<0.001
350–500	481	23.0	421	21.6	
>500	897	42.9	1188	60.9	
HIV RNA >100 000 copies per ml	574	42.8	608	39.4	0.069
Treatment-naïve	188	9.0	327	16.8	<0.001
Backbone					
Abacavir–lamivudine	302	14.5	1149	59.1	<0.001
Tenofovir–emtricitabine	955	45.7	586	30.1	
Other	833	39.9	209	10.8	
Treatment modification	364	17.4	204	10.5	<0.0001
Treatment failure	10	0.48	2	0.10	0.028
Toxicity					
Total	106	5.07	75	3.85	0.060
Gastrointestinal	6	0.29	19	0.97	0.005
Liver	2	0.10	7	0.36	0.098
Lipids	12	0.57	1	0.05	0.003
Neuropsychiatric	13	0.62	33	1.69	0.001
Kidney	3	0.14	0	0.00	0.251
Hematologic	9	0.43	2	0.10	0.046
Allergy	16	0.77	4	0.21	0.011
IRIS	6	0.29	1	0.05	0.076
Other	39	1.87	8	0.41	<0.0001
Convenience					
Total	210	10.04	92	4.72	<0.0001
Patient's wish	54	2.58	44	2.26	0.502
Physician's decision	94	4.50	26	1.33	<0.0001
Treatment simplification	62	2.97	22	1.13	<0.0001
Pregnancy	3	0.14	11	0.56	0.023
Other	25	2.97	18	1.13	0.399
No information	10	0.48	6	0.31	0.390

IQR, interquartile range; IRIS, immune reconstitution inflammatory syndrome; PWID, people who inject drugs.

multivariable Cox regression analysis was used to investigate risk factors for treatment modification because of any reason and because of adverse events. The following variables were assessed: sex, age, ethnicity, prior AIDS-defining condition, hepatitis C virus coinfection, CD4⁺ cell count, HIV RNA, treatment status, ART backbone (abacavir–lamivudine versus tenofovir–emtricitabine versus other) and INSTI (raltegravir versus dolutegravir).

All patients were censored at 1 year after starting ART if no treatment modification or death had occurred. *P* values < 0.05 were considered statistically significant. All analyses were performed using commercially available software (STATA, version 13.1 for Windows, StataCorp, College Station, Texas, USA).

Results

During the study period from 1 April 2006 to 31 December 2015, 4041 HIV-infected individuals participating in the SHCS started an antiretroviral regimen containing either raltegravir (*n* = 2091) or dolutegravir (*n* = 1950). Baseline characteristics are shown in Table 1. Dolutegravir was mostly combined with abacavir–lamivudine in a single-tablet regimen in comparison with raltegravir being most often combined with tenofovir–emtricitabine.

Of 4041 patients included in this study, 568 (14.1%) patients had modification of their ART because of any reason during the first year of treatment, corresponding to 15.5 [95% confidence interval (CI) 14.5–16.9]

Table 2. Risk factors of modification of an antiretroviral regimen containing raltegravir versus dolutegravir within the first year of treatment because of toxicity or intolerance.

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR ^a	95% CI	P value
Female	1.86	1.39–2.49	<0.001	1.98	1.45–2.71	<0.001
Age, per 10 years older	0.91	0.80–1.04	0.156	0.93	0.81–1.07	0.319
Nonwhite ethnicity	1.00	0.69–1.46	0.986	0.75	0.50–1.13	0.172
Prior AIDS-defining condition	0.86	0.61–1.22	0.405	0.89	0.56–1.41	0.513
HCV-coinfection	0.90	0.64–1.26	0.538	0.80	0.56–1.14	0.221
CD4 ⁺ cells per µl						
<350		Reference			Reference	
350–500	0.89	0.58–1.35	0.573	0.98	0.63–1.49	0.880
>500	0.98	0.70–1.39	0.922	1.07	0.73–1.56	0.735
HIV RNA >100 000 copies per ml	1.45	0.87–2.42	0.157	1.53	0.86–2.71	0.149
Treatment naive	1.07	0.70–1.64	0.739	1.05	0.64–1.70	0.858
Backbone						
Abacavir–lamivudine		Reference			Reference	
Tenofovir–emtricitabine	1.05	0.75–1.47	0.773	0.91	0.63–1.32	0.626
Other	1.07	0.74–1.55	0.701	0.97	0.64–1.49	0.902
Raltegravir versus dolutegravir	1.27	0.95–1.70	0.106	1.30	0.92–1.84	0.140

Hazard ratios in univariate and multivariate analysis. CI, confidence interval; HR, hazard ratio.

^aadjusted for all variables listed.

discontinuations per 100 patient-years. Among them, 364 (17.4%) patients were treated with raltegravir and 204 (10.5%) with dolutegravir (Table 1).

The main reason for treatment modification was convenience ($n=302$) expressed by the patient's wish, physician's decision or treatment simplification, followed by toxicity or intolerance ($n=181$). Only 10 patients under raltegravir (0.48%) and two patients under dolutegravir (0.10%) demonstrated virological failure (Table 1).

In multivariable analysis, risk factors of ART modification within the first year of treatment regardless of the main reason were female sex (hazard ratio 1.28, 95% CI 1.06–1.53, $P=0.009$), younger age (hazard ratio 0.90, 95% CI 0.83–0.98 per 10 years older, $P=0.011$), HIV RNA more than 100 000 copies per ml at baseline (hazard ratio 1.49, 95% CI 1.09–2.02, $P=0.011$), and starting a raltegravir-containing regime (hazard ratio 1.71, 95% CI 1.38–2.08, $P<0.001$; S1 Table. Supplementary material, <http://links.lww.com/QAD/B135>). Among pregnant women, those treated with dolutegravir were more likely to discontinue ART compared with those treated with raltegravir. However, this difference was not statistically significant ($P=0.205$).

Adverse events leading to ART modification within the first year occurred in 4.5% of the patients, corresponding to a discontinuation rate of 4.4 (95% CI 3.6–5.5) per 100 patient-years for dolutegravir and 5.7 (95% 4.7–6.9) per 100 patient-years for raltegravir. This difference did not reach statistical significance ($P=0.11$). In multivariate analysis, the only independent risk factor for ART modification because of toxicity was female sex (hazard ratio 1.98, 95% CI 1.45–2.71, $P<0.001$; Table 2).

Neuropsychiatric complaints, although observed in less than 2% of the patients, were the most commonly reported toxicity adverse events and more frequently in the dolutegravir group [discontinuation rate of 1.83 (95% CI 1.30–2.57) per 100 patient-years] compared with the raltegravir group [discontinuation rate of 0.70 (95% CI 0.41–1.21) per 100 patient-years, $P=0.002$]. In multivariable analysis of the subgroup with neurotoxicity, there was a lower risk of discontinuation for raltegravir compared with dolutegravir (hazard ratio 0.46, 95% CI 0.22–0.96, $P=0.037$; S2 Table. supplementary material, <http://links.lww.com/QAD/B135>).

Gastrointestinal adverse events were the second most common reason for ART modification and reported in 19 dolutegravir-treated patients and only in six patients under raltegravir. Allergies and lipid disorders as reason for ART modification were more frequent in raltegravir (16 and 12, respectively) than dolutegravir (four and one, respectively) patients. There were only seven immune reconstitution syndrome events after initiation of a INSTI-containing regimen, six in the raltegravir group and one in the dolutegravir group ($P=0.076$) (Table 1).

Discussion

The large study, involving 4041 HIV-individuals who have started a raltegravir or dolutegravir-containing ART within the SHCS, illustrates in a real-life setting an overall low rate of ART modification because of adverse events or intolerance for both INSTIs (<5%). The rate of neuropsychiatric adverse events was very low (<2%). There were higher discontinuation rates of dolutegravir (1.7%) compared with raltegravir (0.6%) because of

neuropsychiatric adverse events. The only independent risk factor of discontinuing a raltegravir or dolutegravir containing ART within the first year of treatment because of adverse events was female sex. Importantly, we found an outstanding drug potency with an extremely low rate of treatment failures for both drugs ($<0.5\%$ of the patients).

Our results are somewhat in contrast with those recently reported in the literature [7–9], assigning clearly higher rates of treatment discontinuation because of any adverse events (7.6–13.7%) and neuropsychiatric adverse events (5.6–9.9%) for dolutegravir. One explanation might be the smaller number of patients included in those studies which may contribute to an overestimation of the neuropsychiatric adverse events of dolutegravir. In the study by Hoffmann *et al.* [9], the rates of neuropsychiatric adverse events leading to discontinuation within 12 months was estimated to be 5.6% for dolutegravir, affecting mainly women and older patients, but only 0.7% for elvitegravir and 1.9% for raltegravir. Results from a Spanish cohort of 2021 HIV-infected individuals treated with INSTIs showed a relatively low discontinuation rate of dolutegravir because of neuropsychiatric complaints (2.7 per 100 patient-years) as well, however, only in patients with an abacavir–lamivudine backbone, but not with tenofovir–emtricitabine [11]. In our study neither sex, age, nor the backbone, was associated with discontinuation of dolutegravir compared with raltegravir because of toxicity of the central nervous system.

Very recent data from a North American cohort including 2180 patients receiving dolutegravir and 917 raltegravir did not show an increased risk of psychiatric disorders or ART discontinuations because of psychiatric adverse events related to the use of dolutegravir, although more patients treated with dolutegravir had a psychiatric disease at baseline [12]. This might be explained by the favorable profile of dolutegravir concerning the risk of drug–drug interactions in patients treated with psychiatric medications as well as the convenience of a one-pill regimen in this particular patient population.

Interestingly, female patients in our study showed a higher risk of INSTI discontinuation because of any toxicity adverse event compared with male patients. If different pharmacokinetics or lower body weight may have contributed to higher rate of INSTI-related adverse events in female patients remains hypothetical. Of note, recently, a correlation between plasma concentration of dolutegravir and neuropsychiatric side-effects was shown in a small set of HIV-infected individuals [13].

The sequential introduction of raltegravir and dolutegravir could have impacted on the probability to discontinue raltegravir when dolutegravir was available as alternative ART compound since 2013. After 2013, most patients started ART-containing dolutegravir

($n = 1944$, 79%) compared with raltegravir ($n = 516$, 21%). However, we did not find any difference among multivariate models of the probability to discontinue the integrase inhibitor regardless of the main reason and because of neuropsychiatric side-effects when analyses were restricted to the time period before and after 2013.

Our study has some important limitations: information bias might have occurred, as imprecise coding of the reasons for discontinuation of the ART regime cannot be excluded. However, in case of specific symptoms/adverse effects, the proper reason is relatively easy to capture. The reasons for discontinuation are collected by predefined codes in the SHCS database; thus, more detailed information are lacking. Precise descriptions of the particular symptoms and data of minor side-effects not leading to discontinuation of the ART are not available. Therefore, the real burden of all neuropsychiatric events (including minor events) might be underestimated. Only toxicity data leading to the discontinuation of the ART regime are collected in the SHCS database, which, however, represents a highly valuable and representative endpoint. The raltegravir and dolutegravir group differed in some of the baseline characteristics. In addition, other characteristics than those available in the SHCS could have been associated with adverse events. We did not consider data on adherence to treatment for our analysis, and, finally, no data on plasma concentration of INSTI were available for this study.

The main strengths are the large sample size of our study population, the real-life setting, and the prospective collection of patient data including reasons for ART discontinuation.

In conclusion, our study confirms the excellent tolerability of the INSTIs raltegravir and dolutegravir in the treatment of HIV-infected individuals. Raltegravir or dolutegravir drug toxicity is an infrequent reason for treatment modification. Although neuropsychiatric complaints are indeed observed more frequently in patients on dolutegravir compared with raltegravir, in overall these adverse events remain relatively rare. Patient information and monitoring of adverse events are important for early detection of neurotoxicity. In case neuropsychiatric side-effects occur with dolutegravir, a switch to an alternative INSTI remains a valuable option.

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Members of the SHCS Aubert V, Battegay M, Bernasconi E, Böni J, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Günthard HF (President of the SHCS), Haerry D (deputy of 'Positive Council'), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nicca D, Pantaleo G, Paioni P, Rauch A (Chairman of the Scientific Board), Rudin C (Chairman of the Mother and Child Substudy), Scherrer AU (Head of Data Centre), Schmid P, Speck R, Stöckle M, Tarr P, Trkola A, Vernazza P, Wandeler G, Weber R, Yerly S.

All authors have seen and approved the manuscript and have significantly contributed to the work. M.B. and L.E. conceived the idea for this study. L.E. performed the statistical analysis. M.B., S.E., and L.E. wrote the first draft of the paper. All authors contributed to the overall SHCS study and collection of the data. All authors contributed to the later and final versions of the manuscript.

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Conflicts of interest

S.E. has received educational grants from MSD and Gilead. H.F. has received research grants for his institution from ViiV, Gilead, MSD, BMS, Janssen, and Abbvie. M.C. has received research and travel grants for his institution from ViiV and Gilead. A.C. has received unrestricted educational and research grants from MSD, Gilead and ViiV. P.V. has received fees for his institution for temporary advisory board meetings with pharmaceutical companies including ViiV-Healthcare and MSD. G.H. has received research grants from the Swiss National Science Foundation, SHCS, University of Zurich, Yvonne Jacob Foundation, Gilead Sciences, and Roche; fees for data and safety monitoring board membership from Merck; consulting/advisory board membership fees from Gilead Sciences; and travel reimbursement from Gilead. E.B. has received fees for his institution for

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References

1. EACS. European AIDS Clinical Society: EACS Guidelines 8.2. In: EACS Guidelines 82: European AIDS Clinical Society; 2017
2. Günthard HF, Saag MS, Benson CA, del Rio C, Eron JJ, Gallant JE, *et al.* **Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the international antihiv society-USA panel.** *JAMA* 2016; **316**:191–210.
3. Podany AT, Scarsi KK, Fletcher CV. **Comparative clinical pharmacokinetics and pharmacodynamics of HIV-1 integrase strand transfer inhibitors.** *Clinical Pharmacokinetics* 2017; **56**:25–40.
4. Raffi F, Rachlis A, Stellbrink HJ, Hardy WD, Torti C, Orkin C, *et al.*, SPRING-2 Study Group. **Once-daily dolutegravir versus raltegravir in antiretroviral-naïve adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study.** *Lancet* 2013; **381**:735–743.
5. Clotet B, Feinberg J, van Lunzen J, Khuong-Josses MA, Antinori A, Dumitru I, *et al.*, ING114915 Study Team. **Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naïve adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study.** *Lancet* 2014; **383**:2222–2231.
6. Raffi F, Rachlis A, Brinson C, Arasteh K, Gorgolas M, Brennan C, *et al.* **Dolutegravir efficacy at 48 weeks in key subgroups of treatment-naïve HIV-infected individuals in three randomized trials.** *AIDS* 2015; **29**:167–174.
7. de Boer MG, van den Berk GE, van Holten N, Oryszczyn JE, Dorama W, Moha DA, Brinkman K. **Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice.** *AIDS* 2016; **30**:2831–2834.
8. Kheloufi F, Allemand J, Mokhtari S, Default A. **Psychiatric disorders after starting dolutegravir: report of four cases.** *AIDS* 2015; **29**:1723–1725.
9. Hoffmann C, Welz T, Sabranski M, Kolb M, Wolf E, Stellbrink HJ, Wyen C. **Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients.** *HIV Med* 2017; **18**:56–63.
10. Kirby C, Ovens K, Shaw M, Harweir V, Gilleece Y, Churchill D. **Adverse events of dolutegravir may be higher in real world settings.** In: 22nd Annual Conference of the British HIV Association (BHIVA). Manchester, UK: HIVMed; 2016. pp. 22-23.
11. Llibre JM, Esteve A, Miro JP, Mateo G, Curran A, Podzamczak D, *et al.* **Discontinuation of DTG, EVG/c, and RAL due to toxicity in a prospective cohort.** In: Conference on Retroviruses and Opportunistic Infections CROI. Seattle; 2017
12. Hsu R, Fusco J, Henegar C, Carpio F, Mounzer K, Wohlfeiler M, *et al.* **Psychiatric Disorders Observed in HIV+ Patients Using 6 Common 3rd Agents in OPERA.** In: Conference on Retroviruses and Opportunistic Infections CROI. Seattle; 2017
13. Yagura H, Watanabe D, Nakauchi T, Tomishima K, Kasai D, Nishida Y, *et al.* **Effect of Dolutegravir plasma concentration on central nervous system side effect.** In: Conference on Retroviruses and Opportunistic Infections CROI. Seattle; 2017